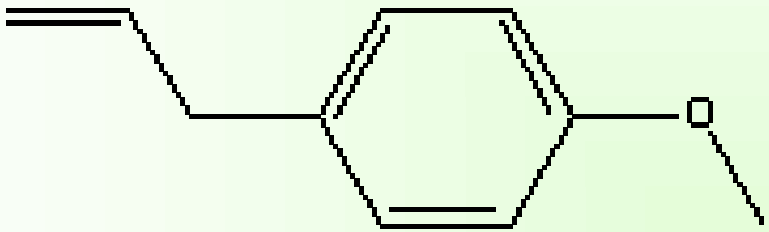
Evidence of the Carcinogenicity of Estragole



Molecular Weight: 148.20 CAS Registry No.: 140-67-0

Use, Production and Occurrence

- Estragole is used for its flavor and fragrant properties in numerous food products, drinks, perfumes, cosmetics, soaps and detergents.
- Production
  - U.S. TSCA >1 million pounds in 1990
  - OECD “high production volume” chemical in 1997
- Major component (30 to 75 %) of volatile oils of anise, basil, bay, tarragon, and other herbs
- Minor component of oils of fennel, marjoram, and chervil, oil of turpentine, and tobacco smoke

Carcinogenicity Studies of Estragole

- Humans
  - No evidence available

- Animals (Drinkwater et al., 1976; Miller et al., 1983; Wiseman et al., 1987)
  - Eight cancer bioassays
  - CD-1, B6C3F_1 , and A/J mice
  - Oral, i.p., and s.c. administration

Carcinogenicity Studies of Estragole

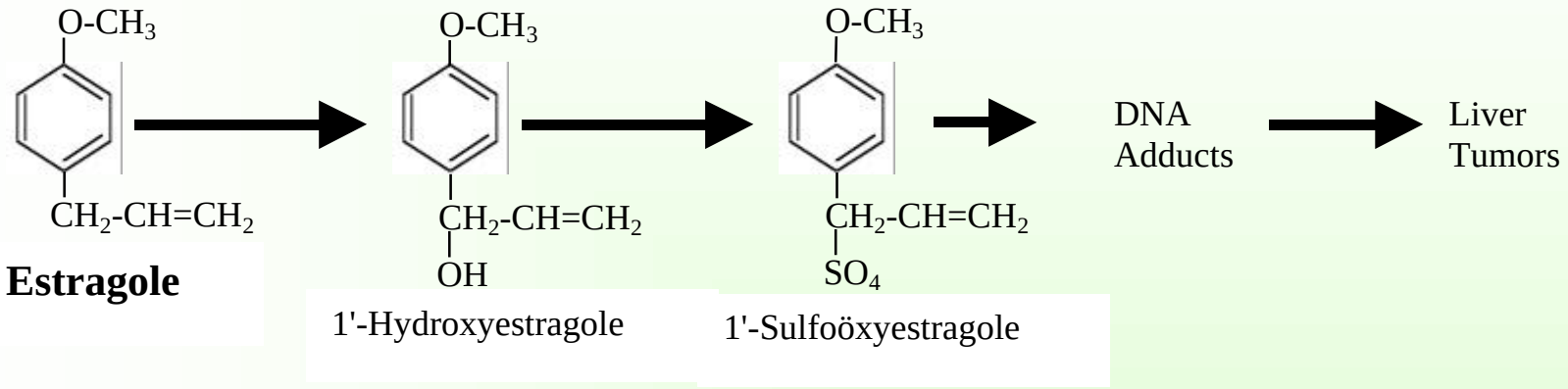
Route of exposure **Test animal**	**Treatment**	**Sacrifice (months)**	**Result[a] (liver tumors)**
oral			
Male newborn CD-1 mice	10 gavage doses	14	+ ($p<0.001$)
Female newborn CD-1 mice	10 gavage doses	14	- ($p=0.16$)
Female CD-1 mice	diet 12 months, 2 dose groups	20	+ ($p<0.001$) + dose-response
i.p.			
Male newborn CD-1 mice	4 doses	12	+ ($p<0.001$)
Male newborn $B6C3F_1$ mice	4 doses	18	+ ($p<0.001$)
Male newborn $B6C3F_1$ mice	1 dose	10	+ ($p<0.001$)
Female A/J mice	24 doses	8	- (lung tumors)
s.c.			
Male newborn CD-1 mice	4 doses, 2 dose groups	15	+ ($p<0.05$) + dose-response

[a] Incidence of hepatocellular carcinoma relative to vehicle controls, except in the A/J mouse study which assayed only for lung tumors.

Carcinogenicity Studies of 1'-Hydroxyestragole, the Putative Toxic Metabolite of Estragole

- 1'-Hydroxyestragole induced high incidences of liver tumors in mice (Drinkwater *et al.*, 1976; Miller *et al.*, 1983; Wiseman *et al.*, 1987)
  - diet for 12 months to adult female CD-1 mice
  - i.p. newborn male CD-1, B6C3F_1, CeH/HeJ, or C57Bl/6J mice
  - s.c. newborn male CD-1 mice
- No increases in tumors in rats given 20 s.c. injections and sacrificed at 24 months

Carcinogenic Mode of Action



- Mechanism is the same as safrole (a Prop. 65 listed carcinogen)
- Six equivalent DNA adducts characterized for estragole and safrole
- Inhibition of the sulfation step significantly reduces DNA adduct formation and prevents liver tumor formation.

Other Relevant Data -- Genotoxicity

- Reverse mutations in *Salmonella*: mixed results for estragole and 1'-hydroxyestragole
- UDS in rat hepatocytes: positive for estragole and 1'-hydroxyestragole
- UDS in human cell lines: positive for estragole and 1'-hydroxyestragole
- DNA adducts and abasic sites observed
- DNA adduct levels in mice in vivo of different alkenylbenzene compounds, including estragole, correlated well with liver tumor incidences

Other Relevant Data -- SAR

- Structural similarities to other many alkenylbenzene compounds observed to be carcinogenic
  - safrole, 1'-hydroxysafole
  - methyleugenol, 1'-hydroxymethyleugenol
  - others: *cis*-asarone, *trans*-asarone, 1'-hydroxy-2',3'-dehydroestragole, 1'-acetoxyestragole, 1'-hydroxy-2',3'-dehydrosafrole, 1'-acetoxysafrole, 1'-hydroxyelemicin, and 1'-acetoxyelemicin

Summary

- Estragole induced liver cancer in multiple strains and both sexes of mice exposed by several different routes of administration.
- Genotoxicity
- Chemical-structural analogies with recognized carcinogens
- Relatively clear understanding of the carcinogenic mode of action